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UNGAR, SUSAN NMN

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/056,230	Applicant(s) Schnitzer
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 6, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above, claim(s) *1, 2, 6, 10, 11, and 15-17* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *3-5, 7-9, and 12-14* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed June 2, 2003 (Paper No. 7) in response to the Office Action of March 25, 2003 (Paper No. 5) is acknowledged and has been entered. Claims 1-17 are pending in the application and Claims 1-2, 6, 10-11, 15-17 and all limitations drawn to inventions other than a method of delivering an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a tissue-specific manner, wherein the agent binds to caveolae, wherein the agent of interest comprises an active agent component and a transport agent component wherein the two components are not the same component wherein the active agent is a drug, the transport component is an antibody and the tissue is pulmonary, lung have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 3-5, 7, 8, 9, 12-14 drawn to a method of delivering an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a tissue-specific manner, wherein the agent binds to caveolae, wherein the agent of interest comprises an active agent component and a transport agent component wherein the two components are not the same component wherein the active agent is a drug, the transport component is an antibody and the tissue is pulmonary, lung are currently under prosecution.

2. Applicant's election with traverse of Claims 3-5, 7, 8, 9, 12-14 drawn to a method of delivering an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side in a tissue-specific manner, wherein the agent binds to caveolae, wherein the agent of interest comprises an active agent component and a transport agent component wherein the

two components are not the same component wherein the active agent is a drug, the transport component is an antibody and the tissue is pulmonary, lung in Paper No 7 is acknowledged. The traversal is on the ground(s) that the inventions are now all drawn to methods which target caveolae and a single search relating to caveolae for transport would provide the relevant references, thus there is not an undue burden on the examiner to search all of the claimed inventions. The arguments have been considered but have not been found persuasive because the literature search, particularly relevant in this art, is not coextensive as drawn to the plethora of tissues, transport agents and active agents claimed. Different searches and issues are involved in the examination of each group. Applicant is reminded that, should claim 3 be found allowable, the restriction requirement as to the linked inventions shall be withdrawn and any claims depending from or otherwise including all the limitations of the allowable linking claim will be entitled to examination in the instant application. Applicant further traverses because the division of the invention into so many groups is unduly burdensome to the Applicant. The argument has been considered but has not been found persuasive because 35 USC 101 specifically states that **a** patent may be obtained for any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof (emphasis added). Thus, Applicant is entitled to the search and prosecution of a single invention. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Specification

3. The specification on page 1 should be amended to reflect the status of the parent applications.

4. The specification on page 49 refers to Supplemental Table 1, no Table 1 was found, no Supplemental Table 1 was found and there is no description of Table 2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

6. Claims 3-5, 7, 8, 9, 12-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn of a method of delivering an agent of interest across a luminal surface of vascular endothelium and from one side of an underlying cell to another side comprising selecting an agent that binds to luminal caveolae, wherein the caveaolaen component to which the agent binds is tissue specific, contacting the luminal surface with said agent, thereby delivering said agent across the luminal surface of vascular endothelium and from one side of an underlying cell to another side in a tissue-specific manner (claim 3), wherein the agent of interest comprises an

active agent component and a transport agent component (claim 4), wherein the tissue is malignant (claim 5), wherein the agent comprises an immunotoxin (claim 7), wherein the active agent is a drug (claim 8), the transport agent component binds to and localizes to a molecule present on the luminal surface of caveolae of the luminal surface of the vascular endothelium (claim 9), wherein the transport agent component is an antibody (claims 12 and 13), wherein the tissue is pulmonary tissue (claim 14). It is noted that inherent in the delivery of a drug to a tissue *in vivo* is the treatment of disease, thus the claims as written read on the *in vivo* treatment of malignancy.

The specification teaches that therapeutic agents must reach target cells in a tissue in sufficient quantities to be potent while sparing bystander organs (p. 2) . The endothelium forms significant barriers that greatly limit the *in vivo* accessibility of many drugs, antibodies to their intended target sites of pharmacological action, namely the cells inside the tissue (p. 2). Molecules residing in caveolae can be targeted by antibodies to caveolar proteins and thereby bring agents conjugated to the antibody into and/or across the endothelium (p. 4). Thus, it is now possible to deliver molecules such as drugs to and/or across endothelial cell membranes (p. 15). In particular, plasma membrane components can be identified which improve transport of a drug such as an immunotoxin to be delivered to a tumor or other malignancy for cancer therapy (p. 16). The specification exemplifies the generation and characterization of a single monoclonal antibody, Mab 833 against a Sprague Dawley rat lung antigen epitope that is expressed in lung but not in other tissues wherein the antigen has a molecular weight of 90 kDA (pp 43-44). *In vitro* assays

clearly demonstrate that in rat lung, Mab 833/Au was found not only on the luminal surface of lung microvasculature, but also was on abluminal surface, and apparently in internalized caveolae and that the gold particles accumulate in the interstitium of the tissue (p. 46). It was found that where attenuated endothelium was in close apposition to the alveolar epithelium, some of the gold particles accumulating in the subendothelial space percolated through the basement member and were taken up by epithelial caveolae for transport into and even across the cell (p. 48). Further, *in vivo* studies confirmed the *in vitro* findings in that Mab 833 targeted the lung endothelial caveolae rather selectively and the label could be detected in luminal, abluminal and cytoplasmic caveolae. Transcytosis was observed with gold particles seen exiting abluminal caveolae to the underlying subendothelial space under normal physiological conditions *in vivo* (p. 49). Thus, a lung-, microvessel-, and caveolae-specific monoclonal antibody which targets the lung *in vivo* has been produced (p. 54) and could be useful as a carrier to achieve tissue specific drug delivery (p. 51). Mab 833 was conjugated to various drugs to assess *in vivo* delivery wherein it was found that daunomycin (an anticancer drug) and dgRA (a highly toxic immunotoxin) were successfully targeted to rat lung (p. 51). When the bioefficiency of the targeted drug was examined using dgRA immunotoxin it was found that the dgRA treated rats showed acute respiratory distress and histological tissue examination revealed lung tissue disruption with edema, blood infiltration and thickening of septa. The damage to lung endothelial and epithelial cells is consistent with endothelial transcytosis of Mab 833 and uptake by underlying tissue cells (p. 51). Finally, the concept of vascular targeting has evolved in the last 20 years from the failure of many directed

therapies to reach their intended target cells (p. 51). Although many attempts have been made to identify tissue-specific targets on vascular endothelium and to develop tissue-specific probes for vascular targeting, directed delivery *in vivo* has not met theoretical expectations (para bridging pages 51-52). Mab 833 as a probe has the specificity and affinity as well as the tissue and cell-selectivity to validate, for the first time, the vascular targeting strategy by achieving theoretical expectations with high-level tissue targeting *in vivo* (p. 52).

One cannot extrapolate the teaching in the specification to the enablement of the claims because although it is clear that Mab 833 is capable of selective and specific delivery of drugs to the caveolae of rat lung microvessels and that the resulting binding results in the transcytosis of the drugs to the subendothelial space and uptake by underlying cells, it is also clear that the uptake of the Mab 833/drug is nonspecific for the lung tissue itself. This is clearly exemplified in the specification wherein the bioefficiency of the targeted drug was examined using dgRA immunotoxin and it was found that the dgRA treated rats showed acute respiratory distress and histological tissue examination revealed lung tissue disruption with edema, blood infiltration and thickening of septa. The specification states that the damage to lung endothelial and epithelial cells is consistent with endothelial transcytosis of Mab 833 and uptake by underlying tissue cells. These results were found after only 24 hours. One would wonders how long it would take the agent of interest to destroy this critical organ and to kill the recipients. In particular, the specification also teaches that therapeutic agents must reach target cells in a tissue in sufficient quantities to be potent while sparing bystander organs. Although it is clear

that Mab 833 as a probe has specificity and affinity as well as the tissue and cell-selectivity for rat lung caveolae, it is equally clear from the information in the specification that the drug delivered across the endothelium does not spare "bystander organs", that is cells that do not have disease. In agreement with Applicant's assessment of the state of the specific vascular targeting, WO 93/17715 specifically taught that there was a need to develop novel strategies for the treatment of solid tumors. One approach involves targeting of agents to the vasculature of the tumor, rather than to tumor cells. (p 5, lines 1-5). For tumor vasculature targeting to succeed, antibodies are required that recognize tumor endothelial cells but not those in normal tissues. Although several antibodies have been raised, none has shown a high degree of specificity. Thus, unfortunately, while vasculature targeting presents promising theoretical advantages, no effective strategies incorporating these advantages have been developed (para bridging pages 5 and 6). Clearly, antibody Mab 833 recognizes vasculature in normal tissue. WO93/17715 recognizes the need to develop antibodies that target a specific vasculature, but also recognizes the need to develop antibodies that are specific for the tumor as well. Although Applicant's invention has clearly addressed the first problem, that is targeting to a specific vasculature, the second problem, that is of tumor specificity has not been addressed. Further, although the invention overcomes the endothelium barrier in rat lung that greatly limits the *in vivo* accessibility of many drugs, antibodies to their intended target sites of pharmacological action, namely the cells inside the tissue, this is not sufficient to enable the claimed invention because the delivery of the drugs as claimed and taught is nonspecific once they have crossed the barrier. The

specification clearly shows that the effects of the drug are nonspecific, that is they kill all of the tissue to which the drugs come in contact. Although the specification contemplates the therapeutic use of the method and the method is used to deliver a drug to malignant tissue and therefore is clearly drawn to *in vivo* therapy of malignant tissue, the method as taught and claimed cannot be used therapeutically, since the clear purpose of therapy is to treat a condition, not kill the patient. Further, even if the agent of interest does not kill all of the cells in lung and somehow finds its way to malignant cells, the specification does not provide guidance as pertains to the appropriate doses and conditions necessary to carry out the two-step process. Given that once the Mab/drug is across the endothelial barrier it is non specific it would be expected that the agent of interest would be sequestered by all cells within the tissue and it is not clear how a sufficient concentration of the agent of interest will be delivered in particular to malignant cells in order to effectively treat the malignancy. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

7. If Applicant were able to overcome the rejection under 35 USC 112, first paragraph above, Claims 3-5, 7, 8, 9, 12-14 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering an agent of interest comprising Mab 833 across a luminal surface of

vascular endothelium from one side of an underlying cell to another side in rat lung by binding to a component of caveolae on the luminal surface of the vascular endothelium does not reasonably provide enablement for a method of delivering an agent of interest across a luminal surface of vascular endothelium from one side of an underlying cell to another side in a tissue specific manner by binding to a component of caveolae on the luminal surface of the vascular endothelium in a tissue.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The claims are drawn to a method of delivering an agent of interest across a luminal surface of vascular endothelium from one side of an underlying cell to another side in a tissue specific manner by binding to a component of caveolae on the luminal surface of the vascular endothelium in a tissue. This means delivering any agent of interest across any luminal surface of vascular endothelium in any tissue in any animal.

(A) As drawn to the agent of interest, the specification discloses a single rat lung, microvessel, caveolae specific monoclonal antibody, Mab 833 which targets the rat lung *in vivo*. The specification teaches that directing delivery of a drug or other agent which is to enter a cell through the action of caveolae can be carried out using an antibody which has a relatively high affinity interaction with a component of caveolae. The specification further teaches the development of Mab 833 wherein twenty stable clones were established and it was found that only two of the clones had relative specificity for lung. Upon further study it was found that one of these

antibodies was not specific for lung but rather bound not only to lung but also was taken up in kidney, adrenal gland and spleen and therefore was not specific for lung caveolae. Finally, the specification teaches that the concept of vascular targeting has evolved in the last 20 years from the failure of many directed therapies to reach their intended target cells (p. 51). Although many attempts have been made to identify tissue-specific targets on vascular endothelium and to develop tissue-specific probes for vascular targeting, directed delivery *in vivo* has not met theoretical expectations (para bridging pages 51-52). Mab 833 as a probe has the specificity and affinity as well as the tissue and cell-selectivity to validate, for the first time, the vascular targeting strategy by achieving theoretical expectations with high-level tissue targeting *in vivo* (p. 52). Given the above, one cannot extrapolate the teaching of the specification to the scope of the claims because it is clear that the identification of Mab 833 as a rat lung specific binder to a component of rat lung caveolae was a hoped for but unexpected event since in 20 years of research by the combined efforts of those skilled in the art, this type of effective specificity had not been previously attained. Given the state of the art as described by the specification, it is clear that one of skill in the art would be forced into undue experimentation to practice the claimed invention.

(B) As drawn to the animal in which the invention may be used, it appears that the identity of the 90 kDa antigen binds is unknown. Thus it is clear that species homologs of the antigen are also unknown. Further, Examiner takes note that species homologs, although they frequently have evolutionarily conserved regions, also are divergent from each other. For example, Winkler et al (UCLA Symposia on

Molecular and Cellular Biology, New Series (1990), 122 (Mol. Evol.), 29-50) specifically teaches that domestic class I gene cat gene sequences are 81 to 72% homologous with human and share 73-79% sequence identity with mouse (see abstract). Further, Elola et al (Acta Bioquimica Clinica Latinoamericanc, 2000, 34(3)293-330) specifically teach that many mammalian galectins have been sequence and well-characterized in different species, being classified as galectin-1 to galectin-10 according to their sequence homology. Identity between carbohydrate-binding domains from different galectins in a certain mammalian species was found to be about 2-40% while the identity of galactins-1 among the different species was 80-90% (see abstract). These examples serve to demonstrate that differences in sequence of homologous gene products across species were well known in the art at the time the invention was made. Thus, it would be expected that there would be differences in the amino acid sequence of species homologs of the 90KDa antigen. Given these sequence differences, it cannot be predicted, whether the epitope to which Mab 833 binds is evolutionarily conserved or whether it is lung specific in species other than rat. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as broadly claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention. It is noted that this drawn to lung specificity across species can be overcome by the submission of objective evidence demonstrating that Mab 833 binds specifically and selectively, for

example, to human tissue in the same manner that it does so in rat. Applicant is invited to submit said objective evidence.

8. Claims 3-5, 7, 8, 9, 12-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth a method of delivering an agent of interest comprising Mab 833 across a luminal surface of vascular endothelium from one side of an underlying cell to another side in rat lung by binding to a component of caveolae on the luminal surface of the vascular endothelium and therefore the written description is not commensurate in scope with the claims drawn to a method of delivering an agent of interest across a luminal surface of vascular endothelium from one side of an underlying cell to another side in a tissue specific manner by binding to a component of caveolae on the luminal surface of the vascular endothelium in a tissue.

The claims are drawn to a method of delivering an agent of interest across a luminal surface of vascular endothelium from one side of an underlying cell to another side in a tissue specific manner by binding to a component of caveolae on the luminal surface of the vascular endothelium in a tissue.

The specification discloses a single rat lung, microvessel, and rat lung caveolae specific monoclonal antibody, Mab 833 which targets the rat lung *in vivo*. The specification teaches that directing delivery of a drug or other agent which is to enter a cell through the action of caveolae can be carried out using an antibody which

has a relatively high affinity interaction with a component of caveolae. The specification further teaches the development of Mab 833 wherein twenty stable clones were established and it was found that only two of the clones had relative specificity for lung. Upon further study it was found that one of these antibodies was not specific for lung but rather bound not only to lung but also was taken up in kidney, adrenal gland and spleen and therefore was not specific for lung caveolae. Finally, the specification teaches that the concept of vascular targeting has evolved in the last 20 years from the failure of many directed therapies to reach their intended target cells (p. 51). Although many attempts have been made to identify tissue-specific targets on vascular endothelium and to develop tissue-specific probes for vascular targeting, directed delivery *in vivo* has not met theoretical expectations (para bridging pages 51-52). Mab 833 as a probe has the specificity and affinity as well as the tissue and cell-selectivity to validate, for the first time, the vascular targeting strategy by achieving theoretical expectations with high-level tissue targeting *in vivo* (p. 52). Given the above, it is clear that the identification of Mab 833 as a rat lung specific binder to a component of rat lung caveolae was an unexpected event. Although the specification suggests that directing delivery of a drug or other agent which is to enter a cell through the action of caveolae can be carried out using an antibody which has a relatively high affinity interaction with a component of caveolae and uses Mab 833 to exemplify the method, it is clear that at the time the invention was made, Applicant did not have possession of the broadly claimed invention which encompasses unidentified agents of interest that bind to

unspecified antigens in unspecified caveolae in unspecified tissues that would be expected to vary substantially in structure and function.

The instant disclosure of a single species of agent of interest does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. Although drawn to the DNA arts, the findings of the court in *Regents of the University of California v. Eli Lilly & Co* is clearly relevant to the instant application. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of agents of interest. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. The specification proposes identifying members of the genus by conventional screening techniques. However, there is no description of the sites at which tissue specific antigens will be found, there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, given the teaching in the specification, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the agents of interest encompassed and no identifying characteristic or property of the instant

agents of interest is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of a single specific agent of interest and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Therefore only a method of delivering an agent of interest comprising Mab 833 across a luminal surface of vascular endothelium from one side of an underlying cell to another side in rat lung by binding to a component of caveolae on the luminal surface of the vascular endothelium, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
August 6, 2003